The Treatment of Furunculosis and Other Staphylococcal Lesions by Staphylococcal Toxoid

By EILEEN O. BARTLEY, M.D., D.P.H.,

from the Department of Bacteriology, Queen's University of Belfast, the Royal Victoria Hospital, Belfast, and the Benn Hospital, Belfast

THE discovery that many strains of staphylococci produce a toxin (Neisser and Wechsberg, 1901[1]; Kraus and Pibream, 1906[2]; Parker, 1924[3]; and Burnet, 1929[4]) has thrown fresh light on the problem of the treatment of staphylococcal lesions.

From staphylococcal toxin, Panton, Valentine, and Dix (1931)[5] successfully prepared staphylococcal toxoid.

In 1933 Parish[6] found that staphylococcal toxoid was innocuous to laboratory animals and was an efficient immunizing agent, causing an increase in the circulating antibody. Parish, O'Meara, and Clarke[7] published the results of further investigations in 1934. They found that the sera of numerous laboratory animals and human subjects contained appreciable amounts of natural anti-toxin.

Staphylococcal toxoid was first used clinically in the treatment of staphylococcal lesions by Panton and Valentine (1932)[8], and by Dolman (1933).[9] The results they obtained were sufficiently encouraging to induce other workers to investigate its effect in the treatment of various lesions due to the staphylococcus. Among these were Connor[10] in Australia, Dolman[9] in Canada, and K. S. Murray[11] in England. Their results, based on the treatment of a large number of cases, made it evident that in staphylococcal toxoid, a rational and reasonably successful method has been made available for the treatment of the chronic and resistant infections due to this organism.

The series of observations on which this article is based was begun in December, 1934, and since then ninety-eight cases have been treated.

CLINICAL RESULTS OF TREATMENT.

The cases have been classified into four groups according to the clinical result obtained. These groups are :—"Recovered," "Markedly Improved," "Improved," and "Unaltered."

Those classified as recovered were the patients whose lesions completely disappeared during the course of treatment. They were not regarded as cured until their condition had remained perfectly satisfactory for at least six months after the conclusion of treatment.

TABLE I.

SUMMARY OF RESULTS.

Result	*Number of cases*	*Percentage*
Recovered - - -	21	30.8
Markedly improved - -	25	36.7
Improved - - -	16	23.5
Unaltered - - -	6	8.8

On consideration of these results, it is evident that ninety-one per cent. of the cases treated derived benefit from the treatment, and that in thirty per cent. of all cases the treatment proved completely successful.

Many of the cases classified as "Markedly improved" have been so grouped because, although their lesions have quite disappeared, their treatment only ceased within the last six months. In six cases, or 8.8 per cent., the treatment was a complete failure. In a few cases relapses occurred some time after the conclusion of their treatment, but on receiving a second course of injections, the lesions again cleared up, and since then the patients have remained well.

A few cases had recrudescences during the course of treatment, but eventually their condition showed a definite if slight improvement. Apart from the disappearance of the local lesion, patients often experience an increased sense of well-being during treatment. Fifteen of them volunteered the information that their appetites had improved; they felt more energetic and better in general health since beginning the course of injections. The beneficial effect on the health of the children treated was especially noteworthy.

TABLE II.

RESULTS IN MORE DETAIL.

Lesion	*Recovered*	*Improved*	*Unaltered*	*Total*
Acne Keloid -	—	1	1	2
Acne with Staph. -	—	11	1	12
Boils - -	17	11	1	29
Dermatitis - -	1	2	—	3
Meibomian Cysts -	—	2	—	2
Styes - -	5	1	—	6
Sycosis Barbæ -	2	3	2	7

On consideration of the results obtained in various clinical conditions, we find that most success is attained in cases of recurrent furunculosis. Twenty-nine cases of boils were treated; seventeen of these made a complete recovery, eight showed marked improvement, and three showed only slight improvement. The boils usually disappear after two or three injections, and do not recur. Some cases improve more slowly; the lesions as they occur become more and more superficial and heal faster, until they finally cease to appear. It has been noted that in these cases fresh lesions may appear two to three days after the weekly injection, especially during the first two or three weeks, although there may be no other evidence of reaction.

The results obtained in acne with staphylococcal infection have proved disappointing. Of twelve cases, none could be described as cured, though all except one showed improvement. The percentage of relapses was high.

Seven cases of sycosis barbæ are included in this series. Two of them remained unaltered by the treatment, but the others were definitely improved, two of them having remained free from trouble for several months.

Good results have been obtained in the treatment of styes. Of six cases treated,

five became completely free from lesions and the sixth improved to a slight degree. Some of these cases were of long standing.

A few cases of blepharitis were treated with satisfactory results, and two cases of meibomian cysts yielded to treatment after a prolonged course of injections. Both these patients need a small course of two or three injections at intervals of a few months in order to keep their lids in a normal condition. In one of them the condition had been present for five years before treatment by toxoid was begun.

Dolman (1935)[12] states that he obtained good results in patients with staphylococcal infections of the nose and nasal sinuses. Three cases in the present series had such an infection, two of them combining the nasal infection with pustules and dermatitis around the nose and upper lip. These two patients did very well, making a complete recovery after a prolonged course of treatment. The third had only a few injections, without any change in his nasal discharge or chronic pharyngitis.

In two cases of furunculosis a certain degree of improvement took place during the course of treatment, but although treatment was continued they made no further progress. When, however, treatment was stopped, they made a quick recovery. This effect has also been noted by Murray (1935),[11] and he suggests as an explanation that the staphylococcus has produced a degree of toxæmia which it takes some time for the circulating anti-toxin to overcome.

Since infection with the staphylococcus is almost universal, it is not unlikely that a great deal of minor ill-health should be due to the toxic effects of its products. That this is probable is shown by the marked improvement in general health which often occurs during a course of injections of staphylococcal toxoid.

Method of Treatment.

The preparation of staphylococcal toxoid used was that supplied by Burroughs, Welcome & Co. It is supplied in two strengths, one ten times stronger than the other. Patients were generally given a course of six to eight injections, beginning with a dose of 0.1 or 0.2 c.c. of the dilute toxoid. The injections were given intramuscularly, at weekly intervals, and the doses were increased progressively according to whether reactions followed their administration or not. Murray[11] and Dolman[9] both recommend an initial dose of 0.5 c.c. of dilute toxoid. This we have found to be too strong an initial dose, as in several of our cases it gave rise to a marked general disturbance. We find that very small doses give rise to no other disturbance than a slight soreness at the seat of injection.

The course of injections given in most cases was 0.2, 0.5, and 0.75 c.c. of the dilute toxoid, followed by 0.1, 0.2, and 0.4 of the strong toxoid. In some cases this plan could not be followed because of the marked general reactions which occurred in these patients even when small doses were given. Consequently treatment by the small doses tolerated had to be continued over a longer period, up to nineteen doses having been given in a few instances. This prolonged method of treatment was also adopted in those patients whose lesions were slow in improving. In both types of case the results obtained were satisfactory.

The dosage depends upon the individual patient and his reaction to toxoid. One has to be guided by the individual and his response just as in giving vaccines. For example, one patient could tolerate a dose of only 0.3 c.c. of dilute toxoid, but as the result of fifteen injections he made a complete recovery from a long-standing furunculosis.

Reactions.

Notes of reactions were made in forty-three cases. Of these, sixteen, or thirty-nine per cent., observed no reaction whatever. The usual type of reaction which occurred was a slight soreness and stiffness at the site of injection; this can be disregarded from the point of view of increase of dosage. It was accompanied in twenty-five per cent. of cases by a mild general reaction, the patients complaining of headache and malaise which occurred during the evening following the injection.

The more severe type of local reaction was characterized by tenderness, swelling, and redness at the site of injection. The needle puncture was surrounded by an area of redness sometimes up to three inches or more in diameter. This appeared twelve hours after the inoculation, and lasted two or three days. Often it was accompanied by headache.

Severe general reactions occurred in seven cases, or sixteen per cent. of the patients treated. There was very marked malaise with severe headache, general aching, restlessness, and sleeplessness. These symptoms came on some hours after the injections, and sometimes continued into the following day, although they became less severe as time went on. There was probably a rise in temperature, although temperatures were not recorded.

Nausea and giddiness occurred in a few cases, and one or two patients complained of a feeling of nausea which lasted for some days.

In two patients the first injection (of 0.5 c.c. dilute toxoid) had rather a curious effect. Three hours after the injection of toxoid their vision became blurred and they were unable to see print or even large objects clearly. The condition passed off in half an hour, and was followed by headache. A third patient had similar symptoms, but in a lesser degree, and in his case it was accompanied by itching of both eyes. This man had a much smaller initial dose than the other two.

If the initial dose is small, and care is taken not to increase the dose too rapidly, reactions give rise to very little trouble.

Several children have been treated in our series, and in none of them did any reactions occur, thus confirming Dolman's statement (1935)[12] that in children the inoculations give rise to very little discomfort.

Dolman (1935)[12] also states that the tolerance which adults develop to later doses is soon lost, and if a lapse of one month has occurred since the last dose of toxoid, the initial dose of any supplementary course should not be more than 0.1 c.c. of the strong toxoid. Our results confirm this finding, and in addition we have found that during the course of prolonged treatment it is sometimes necessary to reduce the dose, as the patient may begin to show reactions to a larger dose if it is continued over a number of weeks.

In six cases an exacerbation of the local lesion followed the first one or two injections.

Effect of the Inoculation of Staphylococcal Toxoid upon the Circulating Anti-toxin.

The total number of cases treated and followed up was sixty-eight. In almost all cases the amount of circulating anti-toxin in the blood was estimated before treatment. Estimations were carried out on ninety-five sera taken from patients before treatment was begun, and the average amount of anti-toxin present in these sera was found to be one international unit. The method used for this estimation was that devised by Parish, O'Meara, and Clarke[7] in 1934. It consists in the titration of the amount of anti-toxin present in a serum, the result being expressed in terms of international units. (Parish—personal communication.)

Table III.

Units of Circulating Anti-toxin in the Blood Before and After Treatment.

Number of cases treated	*Units before treatment*	*Units after treatment with six to eight doses of toxoid (0.62 c.c.)*
68	1	7.7

The result shown in the above table is in accordance with Murray's observation that four doses of toxoid increase the initial value of the circulating anti-toxin almost eightfold. The figures given are the averages calculated from these sixty-eight cases.

Table IV.

Units of Circulating Anti-toxin in the Blood Before and After Treatment in Different Clinical Conditions.

Cases	*Average initial titre*	*Average titre after six to eight weeks treatment*	*Average amount toxoid given*
Acne Keloid -	1	5	0.96 c.c.
Acne with Staph.	0.75	8	0.45 c.c.
Boils - -	1	5	0.79 c.c.
Dermatitis -	2	10	0.57 c.c.
Meibomian Cysts -	1	5	1.55 c.c.
Styes - -	0.4	8	0.57 c.c.
Sycosis Barbæ -	2	8	0.5 c.c.

From this table it may be deduced that the increase of circulating anti-toxin is not affected by the type or situation of the staphylococcal infection. Also, the increase in the circulating anti-toxin bears no relationship to the amount of toxoid given.

As regards the production of anti-toxin, it was also noted that two main types of response could be distinguished. Some patients acquire anti-toxin very slowly,

reach a comparatively low titre (three units), and lose their acquired anti-toxin equally slowly. On the other hand, some respond quickly, reach a high titre in a short time (up to thirty-eight units has been noted), and lose their acquired anti-toxin almost as quickly as they produce it.

Clinically, the members of the first group seem to have somewhat better results than those of the second group, but the numbers are not large enough to allow of definite conclusions being drawn.

TABLE V.

RESULTS SHOWING THE AVERAGE INCREASE OF ANTI-TOXIN IN EACH GROUP.

Result	*Units before treatment*	*Units after treatment*
Recovered - - -	0.75	9.3
Markedly improved - -	1.5	8
Slightly improved - -	0.75	11
Unaltered - -	0.4	5

On the whole, there is no relationship between the anti-toxin produced and the clinical result, as is shown in Table V.

The effect of the prolonged injection of toxoid was noted in twenty-three cases. Frequent estimations of the anti-toxic content of the blood of these patients were carried out. In nine of them a continuous increase of circulating anti-toxin was produced, but in the remaining fourteen there was either no change or an actual fall in the anti-toxic content of the blood. The average fall observed was from eleven units to three units. It was found that the anti-toxic titre of the blood always falls when treatment is stopped, but it seldom or never reaches its original level, and, indeed, seldom goes below two or three units in amount.

In those cases liable to recurrences, the estimation of the anti-toxic content of the blood is useful, because it enables us to determine if and when a further course of treatment is advisable. It also serves as a guide in the treatment of those cases which need a small dose every two or three weeks to keep them free from lesions.

VACCINE TREATMENT.

Almost all the patients who came for treatment with staphylococcal toxoid had had previous courses of vaccines, either stock or autogenous. In most of these cases vaccine treatment was quite without results; in a few it was responsible for a temporary recovery, but was without effect on being tried a second time.

A possible explanation of the occasional success of vaccine therapy may be found in the observation made by Burnet (1930),[13] and confirmed by Parish, O'Meara, and Clarke,[7] that the toxins produced by different strains of staphylococcus aureus vary in potency. If, therefore, the strain of staphylococcus aureus used to make the vaccine is a highly toxigenic one, that may account for its success when used in vaccine therapy.

With regard to the effect of vaccine therapy on the amount of circulating anti-toxin in the blood, it was found that the average amount present in the bloods of

all those who had had vaccines was 0.89 units, while the average amount present in the bloods of those who had been treated with autogenous vaccines was two units.

Inoculation by staphylococcal toxoid marks a distinct advance in the treatment of staphylococcal lesions, but much further work remains to be done in the investigation of other products of the staphylococcus. Evidence is accumulating to show that there is more than one toxin produced by the staphylococcus, and also that this organism produces other substances which are concerned in infection and immunity. The polyvalency of the staphylococcal toxins may account for some of the failures in treatment which are at present inexplicable.

Summary.

1. The inoculation of staphylococcal toxoid produces an increase in the antitoxin circulating in the blood.

2. In ninety per cent. of the cases treated, definite improvement of their clinical condition resulted.

3. Six per cent. of cases showed no response.

4. Reactions following inoculations are not troublesome if the plan of giving an initial dose of 0.1 or 0.2 c.c. of dilute toxoid is adhered to.

5. The general health of patients often shows marked improvement.

6. Children respond well, and reactions are not troublesome in their cases. The same dosage was given no matter what the age of the patient.

7. Patients suffering from furunculosis, dermatitis, and styes are most likely to have a favourable result.

I have much pleasure in acknowledging the willing help and co-operation of Dr. McCaw, Dr. Lewis, and Dr. N. C. Graham in the carrying out of this work.

References.

1. Neisser, M., and Wechsberg, F., *Zeits. f. Hyg. u. Infectionsk.*, 1901, Vol. 36, p. 299.
2. Kraus and Pibream, *Wien. klin. Woch.*, 1906, Vol. 19, p. 493.
3. Parker, *Journ. Exper. Med.*, 1924, Vol. 40, p. 761.
4. Burnet, F. M., *Journ. Path. and Bact.*, 1929, Vol. 32, p. 717.
5. Panton, P. N., Valentine, F. C. O., and Dix, V. W., *The Lancet*, 1931, 2, p. 1180.
6. Parish, H. J., *Brit. Med. Journ.*, 1933, 2, p. 277.
7. Parish, H. J., O'Meara, R. A. Q., and Clarke, W. H. M., *The Lancet*, 1934, 1, p. 1054.
8. Panton, P. N., and Valentine, F. C. O., *ibid.*, 1932, 1, p. 506.
9. Dolman, C. E., *Journ. Amer. Med. Assoc.*, 1933, 100, p. 1007.
10. Connor, *Brit. Med. Jour.*, 1935, 2, p. 1195.
11. Murray, K. S., *The Lancet*, 1935, 1, p. 303.
12. Dolman, C. E., *ibid.*, 1935, 1, p. 306.
13. Burnet, F. M., *Journ. Path. and Bact.*, Vol. 33, 1930, p. 315